REMission INDuction in very early Rheumatoid Arthritis

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To investigate whether tapering MTX first, then the TNFi golimumab (GOL), is more efficacious than tapering GOL first, then MTX, in sustaining remission and reaching drug free remission.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Synovial and bursal disorders
Study type	Interventional

Summary

ID

NL-OMON47431

Source
ToetsingOnline

Brief title
REMINDRA

Condition

- Synovial and bursal disorders

Synonym
Arthritis, RA

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: MSD

Intervention

Keyword: Remission, Rheumatoid arthritis, Taper, TNF-inhibitor

Outcome measures

Primary outcome

The primary end point is the proportion of patients in sustained remission at week 24 after start of tapering of either MTX or GOL first.

Secondary outcome

Phase I (Remission induction):

- The proportion of patients on MTX/HCQ/GC in remission, defined as DAS28<2.6, at week 12 or week 24 after start of treatment.

- The proportion of patients on MTX/GOL in sustained remission, defined as DAS28<2.6 with max 4 swollen joints of the 44SJC at 2 consecutive visits 3 months apart, at week 24 after start of GOL treatment.

- Predictors of remission upon treatment with MTX, HCQ and a single injection of i.m. GC (e.g. smoking status, BMI, alcohol use, sex, disease duration, DAS28, RF-status, ACPA-status, presence of erosions)

- Predictors of remission upon treatment with MTX and GOL (e.g. smoking status, BMI, alcohol use, sex, disease duration, DAS28, RF-status, ACPA-status, presence of erosions)

Phase II (Tapering):

- The proportion of patients in sustained remission, defined as DAS28<2.6 with max 4 swollen joints of the 44SJC at 2 consecutive visits 3 months apart, at week 48 after start of tapering MTX first, then GOL or GOL first, then MTX.

- The proportion of patients in drug-free sustained remission, defined as DAS28<2.6 with max 4 swollen joints of the 44SJC at 2 consecutive visits 3 months apart while off anti-rheumatic treatment, at week 48 after start of tapering
- Mean disease activity, using the disease activity score assessing 28 joints (DAS28), at week 24 and week 48 after start of tapering
- Mean functional ability, using the Dutch consensus health assessment questionnaire (HAQ), at week 24 and week 48 after start of tapering
- Mean quality of life, using the visual analogue scale (VAS) of the EuroQol 5 dimensions (EQ5D) questionnaire, at week 24 and week 48 after start of tapering
- Mean anxiety and depression (using the Hospital Anxiety and Depression Scale (HADS)), at week 24 and week 48 after start of tapering
- Mean fatigue (using the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F)), at week 24 and week 48 after start of tapering
- The frequency of serious adverse events (SAEs) between the two tapering strategies after 24 and after 48 weeks.
- The time until remission (DAS28<2.6) after retreatment with the last effective dose upon flare while tapering MTX/GOL.

Phase III (Follow-up):
- The proportion of patients in drug-free sustained remission, defined as DAS28<2.6 with max 4 swollen joints of the 44SJC at 2 consecutive visits 3 months apart while off anti-rheumatic treatment, at week 48 after discontinuation of both MTX and GOL

- The time until remission, defined as DAS28<2.6, after retreatment in clinical care upon flare

- The proportion of serious adverse events (SAEs) between the two tapering strategies at week 24 and week 48.

Phase II and III:

- Cost per extra patient in remission up to week 96 after start of tapering (end of phase III)

- Cost per Quality Adjusted life Year (QALY) gained up to week 96 after start of tapering (end of phase III)

Overall:

- The predictive value of the patient reported Routine Assessment of Patient Index Data 3 (RAPID3, performed monthly) to detect DAS28-remission and -flare (evaluated 3-monthly).

Study description

Background summary

Rheumatoid arthritis (RA) patients in remission with a combination of TNFinhibitors (TNFi) and methotrexate (MTX) often express their wish to stop MTX treatment because of side effects. Given the efficacy of TNFi it is conceivable that in early RA patients in remission with methotrexate (MTX)/TNFi stepwise discontinuation of MTX prior to TNFi is superior in maintaining sustained remission and reaching drug free remission as compared to discontinuation of TNFi prior to MTX.

Study objective

To investigate whether tapering MTX first, then the TNFi golimumab (GOL), is more efficacious than tapering GOL first, then MTX, in sustaining remission and reaching drug free remission.

Study design

We will perform a multicenter, open label clinical trial in very early RA patients. Remission will be induced by an open label T2T remission induction protocol in clinical care. Patients in sustained remission on MTX/GOL will be randomized to taper either MTX first, then GOL or GOL first, then MTX.

Intervention

Remission will be induced by a combination of MTX, hydroxychloroquine (HCQ), i.m. glucocorticoids (GC), and, if not in remission, the TNFi golimumab (GOL) (phase I).

Patients in sustained remission on MTX/GOL at the end of phase I (after 24 weeks of treatment with MTX/GOL) will be randomized in a ratio of 1:1 to taper medication as follows:
- Group A: Taper and stop GOL first during 24 weeks, then, if still in sustained remission, taper and stop MTX during 24 weeks
- Group B: Taper and stop MTX first during 24 weeks, then, if still in sustained remission, taper and stop GOL during 24 weeks

During 1 year additional follow-up maintenance of drug-free sustained remission will be investigated (phase III).

Study burden and risks

The study visits will be performed in combination with 3-monthly scheduled visits to the outpatient clinic in usual care. Patients will be treated according to a treat-to-target strategy. In addition to usual care, patients will fill in questionnaires: HAQ, EQ-5D, HADS, FACIT-F, RAPID3, and a health care utilization and work participation questionnaire. No increased risks are associated with the randomised tapering strategy as clinical studies performed so far have shown reasonable results for tapering TNFi for patients in remission. Importantly, remission can be reached again in most of the patients who flare during the tapering phase or after withdrawal of TNFi after retreatment. This is current clinical practice. Moreover, patients tapering or discontinuing MTX during TNFi treatment generally have comparable DAS28 scores and TNFi drug survival as those who continue MTX treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:
- Able and willing to give written informed consent
- At least 18 years of age
- Fulfilling 2010 ACR/EULAR criteria for RA (Appendix A.)
- Patient reported symptom duration (joint stiffness, tenderness, pain, and/or swelling) < 12 months
- Naïve for DMARD and biological treatment
- DAS28 <=>3.2
- Have sufficient knowledge of the Dutch language to be able to comply with the requirements of the study protocol

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Having used glucocorticoids < 6 weeks before the baseline visit
- Being pregnant (based on anamnesis) or a nursing women or a women of child bearing potential without (adequate) use of contraception
- Having any other inflammatory rheumatic disease than RA, except for secondary Sjögren*s syndrome
- Having contraindications for the use of MTX/HCQ/methylprednisolone/GOL.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-05-2017
Enrollment:	267
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Plaquenil
Generic name:	Hydroxychloroquine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Simponi
Generic name:	Golimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-09-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-10-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	25-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-004858-17-NL
CCMO	NL55647.041.16